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Original Article

Spectrum and Frequency of Adverse Drug Reactions to First Line Anti-Tuberculous Drugs

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ABSTRACT

The current first-line drugs used for Tuberculosis treatment are reported to cause adverse effects. Inconvenience caused by ADRs can lead to discontinuation of therapy, inducing drug resistance. ADRs, when not appropriately managed, cause significant morbidity and mortality. A Prospective observational study was conducted comprising of 192 patients presenting to Pulmonary Medicine Department and NTEP cell, Government General Hospital, Vijayawada, to identify the spectrum and evaluate frequency of Adverse reactions in patients, using first-line anti-tuberculous drugs. Among 192 patients using first-line Anti-Tuberculous Drugs, 56 patients (29.1%) developed at least one Adverse drug reaction. The most common organ system associated with adverse effects in the study was Gastro-intestinal (25, 44.6%). Other major organ systems the effects were attributed to are Hepatobiliary system (12, 21.4%) and cutaneous (11, 19.6%). The most common adverse effect identified was Nausea/Vomiting (22, 39.2%). Other major side effects were abdominal pain (10, 19.6%) and pruritus (8, 14.3%). Although majority of ADRs could be managed by symptomatic treatment, severe ADRs require discontinuation of regimen and sequential re-introduction. Most of the patients tolerated well to sequential re-introduction of drugs while minority required alteration in regimen.

Keywords*: Adverse Drug Reactions, Anti-Tuberculous drugs, First-line, Prevalence, Management.*

INTRODUCTION

The current first-line drugs used in the Drug sensitive regimen for the treatment of Tuberculosis in India, include Rifampicin(R), Isoniazid(H), Pyrazinamide(Z) and Ethambutol(E). The prevalence of ADRs for these Anti-tuberculous drugs reported in various studies conducted across the world, ranged from 8% to 85% [1]. These adverse drugs reactions have a wide spectrum, including but not limited to Gastritis, Dermatitis, Hepatitis, Acute Kidney Injury, Peripheral neuropathy, Arthritis, Psychosis, Hearing loss, Haematological abnormalities and Optic neuritis [2]. Adverse reactions of these drugs are of a major concern, as they can contribute to discontinuation and sub-optimal adherence to therapy, inducing drug resistant tuberculosis. When not appropriately managed, either by symptomatic therapy or alteration of the drug regimen, adverse effects can lead to significant morbidity and in some cases mortality [3]. The current study aims to identify the spectrum of Adverse drugs effects of first-line anti-tuberculous drugs and evaluate the frequency of each of these effects.

MATERIALS AND METHODS

A prospective observational study was conducted for the period of 12 months (from September 2024 to August 2025) in the Department of Pulmonary Medicine, Siddhartha Medical College, Vijayawada after obtaining ethical clearance. The

objective of the study was to evaluate the spectrum of adverse drug reactions to First Line Anti-tuberculous drugs and identify their frequency. A sample of 192 patients, presenting to our department, using first line Anti-tuberculous drugs, were included in the study after obtaining a written consent. A detailed clinical history and history of adverse effects was taken from the patients and they were followed for the duration of their treatment. Additional treatment and hospital admission were provided to the patient as and when required during the course of the study.

Inclusion criteria

- Age > 18 years
- Willingness to participate in the study
- Patient on Drug Sensitive regimen for PTB and EPTB

Exclusion criteria

- Age < 18 years
- Patient on Drug resistant (H-mono/ poly drug resistant, Multi and Extensively Drug resistant) regimen for Tuberculosis
- Patients not compliant to therapy

RESULTS

A total of 192 patients on first-line Anti tuberculous drugs that participated in the study. 56 of these patients (29.1%) developed at least one ADR, as represented in Fig.1. These patients include 11 cases with Extrapulmonary Tuberculosis and 45 with Pulmonary Tuberculosis.

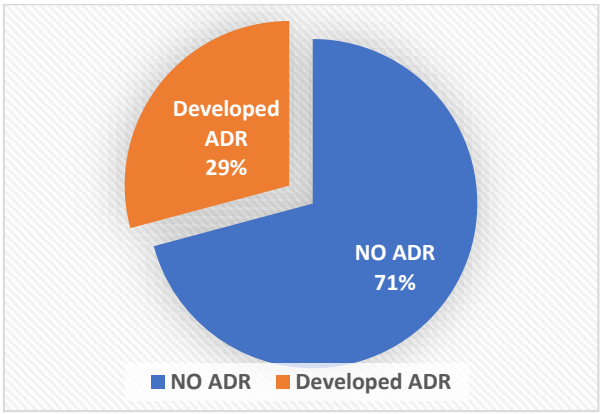

Figure 1: Frequency ADRs to first line anti tuberculous drugs

Among the 56 cases, who developed adverse drug reactions, majority (46 patients, 24% of total participants) developed the reactions in the first two months of therapy (Intensive phase) while minority (10 patients, 5.2% of total participants) developed the reactions in the next 4 months of treatment (Continuation phase) (Fig.2)

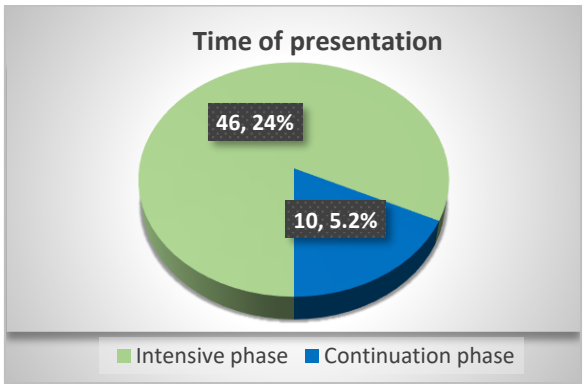

Figure 2: Time of presentation of ADRs to first line anti tuberculous drugs

Among the adverse effects identified, the most common predominant symptom was Nausea/ vomiting seen in 22 patients (11.45%), followed by abdominal pain in 10 patients (5.2%), pruritus in 8 patients (4.1%), Joint aches in 4 patients (2.1%), diminished vision and decreased urine output were seen in 2 patients each (1.04%). Asymptomatic elevation of liver enzymes without clinical jaundice was seen in 5 patients (2.6%). [Fig. 3, Table.1]

Predominant symptom	No. of Patients	% of Study population	% of patients with ADRs
Nausea/ Vomiting	22	11.45%	39.2%
Pruritus	8	4.16%	14.3%
Abdominal pain	10	5.2%	19.6%
Arthralgia	4	2.08%	7.1%
Asymptomatic raised liver enzymes	5	2.6%	8.9%
Decreased urine	2	1.04%	3.6%
Diminished vision	2	1.04%	3.6%
Erythroderma	3	1.56%	5.3%

Table.1: Predominant adverse effects and their frequency in patients using first line anti-tuberculous drugs

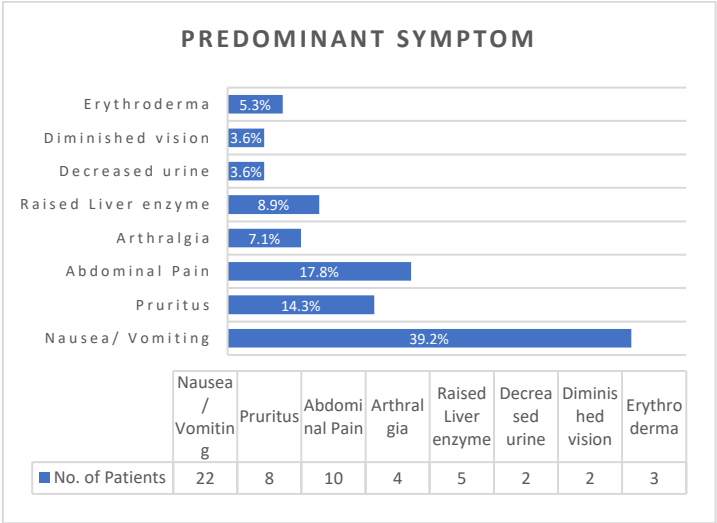

Figure 3: Predominant adverse effects and their frequency in patients using first line anti-tuberculous drugs

The most common major organ system involved, among the patients with adverse drug reactions, was Gastrointestinal system in 25 patients (13%), followed by hepato-biliary in 12 patients (6.25%), cutaneous reactions in 11 patients (5.7%), Musculoskeletal system in 4 patients (2.1%), Renal and Ophthalmic in 2 patients each (1.0% each). [Table 2 & Fig. 4]

System involved	No. of Patients	% of Study population	% of patients with ADRs
Gastro-Intestinal	25	13.02%	44.6%
Hepatic	12	6.25%	21.4%
Skin	11	5.72%	19.6%
Musculo-skeletal	4	2.08%	7.1%
Renal	2	1.04%	3.6%
Ophthalmic	2	1.04%	3.6%

Table.2: Major organ system involved and frequency in patients using first line anti-tuberculous drugs

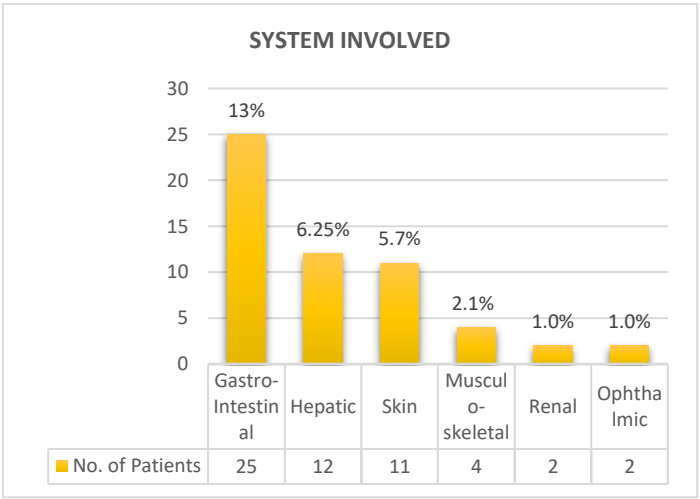

Figure 4: Major organ system involved and frequency in patients using first line anti-tuberculous drugs

Majority of ADRs (37 patients, 65% of ADRs) were managed by symptomatic treatment. Severe ADRs (Erythroderma, hepatitis, optic neuritis) required discontinuation of regimen followed by sequential re-introduction of individual drugs – (19, 35%). Most of the patients, particularly with hepato-biliary effects, tolerated well to sequential re-introduction all the of drugs (9, 16%), however some required alterations in the drug regimen (7, 12%) and few, dose reduction (3, 6%). Fig.5

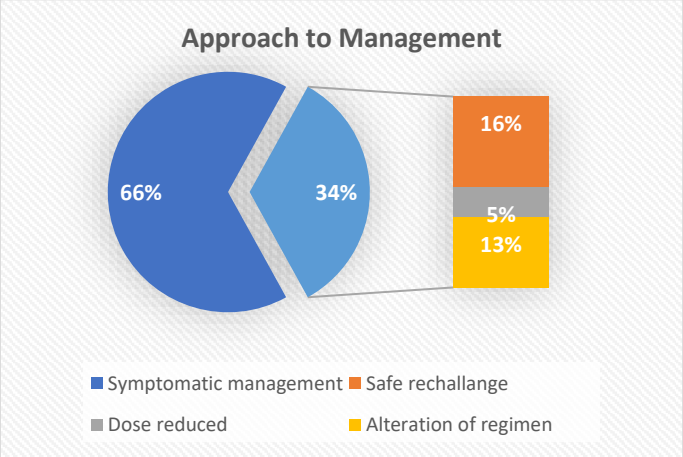

Fig.5: Approach to the management of Adverse drug reactions

DISCUSSION

World Health Organization (WHO) defined adverse drug reactions (ADRs) as, unintended and noxious response to a drug which occurs at doses normally used in a human for the treatment or prophylaxis or diagnosis of a disease or for the modification of physiological function. [7] First-line anti tuberculous drugs used in India, under National Tuberculosis elimination program, are Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. These drugs are associated with a high incidence of a wide range of adverse drug effects. Studies worldwide demonstrated the prevalence of ADRs for first line Anti-tuberculous drugs ranging from 8 – 85%. An Indian hospital-based study by Mandal et.al. observed that the overall toxicity was found in 35% cases in the patients using daily regimen [5]. Taher et.al. in 2006, reported the frequency of ADRs as 29% for first line anti-tuberculous drugs [6]. The adverse effects are varied and multifactorial. The major determinants in occurrence of these effects are reported as elderly age, nutritional status, alcohol consumption, altered liver and kidney function, polypharmacy and HIV infection.

Majority of Adverse drug reactions to first line Anti tuberculous drugs in the current study, occurred during Intensive Phase of treatment. This may be attributed to the fact that, a greater number of drugs used in the Intensive phase of treatment compared to the continuation phase. The results from the current study revealed that the Gastro-intestinal system, Cutaneous and Hepato-biliary system are the most commonly affected organ systems through ADRs, which is in-line with majority of studies worldwide [8].

The adverse effects also show a wide range of severity. Mild adverse effects are more common in occurrence and include gastritis, nausea, joint aches and pruritus. Management approach for these mild adverse reactions ranged from supportive and psychological to pharmacological therapy and symptomatic management [9]. The patients with mild adverse drug reactions did not need any hospital admission for appropriate management.

Severe adverse effects include but are not limited to diminished vision, hepatic failure, renal failure, erythroderma and thrombocytopenia. Hospitalization, for observation of the patient and provision of supportive management, is often required in the management of severe adverse effects. The ideal approach for the management of severe adverse drug effects, is to withhold the drugs, followed by sequential rechallenge to identify the offending agent and consider desensitization of the offending agent. If desensitization is contraindicated or not possible alteration of drug regimen/ dosage reduction should be considered. Prompt identification of the adverse effect followed by appropriate management is necessary in curtailing the morbidity caused by adverse drug reactions.

CONCLUSION

Anti-tuberculous drugs can cause wide range of adverse drug reactions including gastritis, hepatitis, dermatitis, renal failure, arthralgia, optic neuritis, psychosis and seizures. Among these effects, the results of the study revealed Gastritis, Hepato-biliary dysfunction and cutaneous reactions to be the most common reactions. These results on frequency and spectrum of ADRs aligned with the studies by several Indian authors. The adverse drug reactions pose a significant burden to society with increased hospital stays and contributing to the discontinuation of therapy by the patient. Accurate diagnosis of ADR and appropriate management is required to reduce the morbidity and overcome the non-adherence of patients to therapy. Patient counselling and dissemination of the awareness on adverse drug reactions to treatment providers plays an important role in early detection and appropriate management of these reactions.

LIMITATIONS

The study was conducted in a single tertiary centre; hence the results of the study could not be generalized to areas where the population doesn't resemble the study group.

Association of the adverse drug reaction with underlying patient comorbidities and type of tuberculosis could not be assessed in the current study.

List of abbreviations

- ADRs – Adverse drug reactions
- ATT – Anti tuberculous therapy
- EPTB – Extra Pulmonary Tuberculosis
- PTB – Pulmonary Tuberculosis

DECLARATION:

Conflicts of interest: the authors declare no conflicts of interest.
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